Novel Spiro Phosphinite Ligands and Their Application in Homogeneous Catalytic Hydrogenation Reactions

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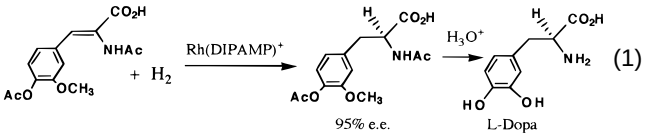
The homogeneous catalytic asymmetric hydrogenation of prochiral olefins is one of the most important advancements in modern organic synthesis.[1] For the asymmetric hydrogenation of prochiral enamides, the use of rhodium catalysts containing chiral phosphine ligands has been found to be the most successful. The successful asymmetric hydrogenation of (*Z*)-2-acetamido-3-(3-methoxy-4-acetoxyphenyl)acrylic acid with $Rh(DIPAMP)^+$ catalyst was developed by Knowles *et al.* to be a commercial process for the production of L-Dopa.[2] More



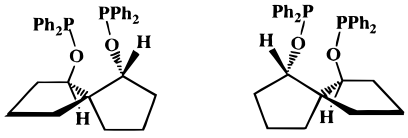
(1)

recently, the development of Rh(BINAP),[3] Ru(BINAP),[4] and Rh(Duphos)[5] catalysts have attracted much attention. In contrast, the development of chiral phosphinite ligands for asymmetric hydrogenation has been less successful.[6] So far no chiral phosphinite ligand has been found to give the same high enantioselectivity as the best chiral phosphine ligands. Recently Selke *et al.* developed a series of aryl 4,6-*O*-(*R*)-benzylidene-2,3-bis(*O*-diphenylphosphino)-β-D-glucopyranosides and found them to be effective chiral ligands for rhodium catalysts in the asymmetric hydrogenation of dehydroamino acid derivatives.[7] The disadvantage of this type of natural-product-based ligand is its chirality being limited by mother nature: the opposite enantiomer of the ligand cannot be easily synthesized because of the unavailability of the appropriate carbohydrate starting materials. This limitation renders the catalyst useless when an opposite enantiomer of the product is desired.

The most important advantage of chiral phosphinite ligands over the corresponding phosphine ligands is the easiness of preparation. The synthesis of phosphinites by reacting the corresponding alcohols with chlorophosphines in the presence of an organic base is very convenient, and the yields are usually quantitative. From a practical standpoint, it is of substantial interest to develop highly effective chiral phosphinite ligands for asymmetric catalysis. In this paper, we report the synthesis, characterization, and application of a novel class of highly effective chiral phosphinite ligands that contain a spiro backbone.

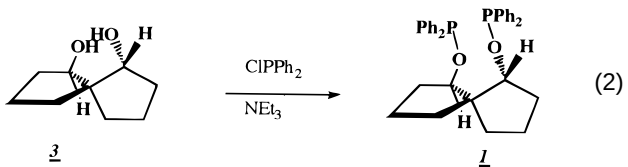
Noyori and co-workers suggested that the highly skewed position of the naphthyl rings in BINAP was the determining factor for the ligand to be so effective in asymmetric catalytic reactions.[8] A comparison of the structure of BINAP with that of the less-effective BINAPO [2,2′-bis(diphenylphosphinoxy)-1,1′-binaphthyl] ligand[6a] reveals two possible reasons for the difference in their effectiveness as chiral ligands in homogeneous catalysis. (1) The oxygen atoms in BINAPO increase the distance between the chiral binaphthyl moiety and the PPh_2 groups and therefore decrease the influence of the binaphthyl functionality on the stereopositions of the phenyl rings of the PPh_2 group. Consequently there is less control of stereoselectivity in the catalyst−substrate interaction. (2) The presence of the C−O−P bond in BINAPO substantially increases the flexibility of the backbone and consequently decreases the enantioselectivity of the catalyst.

In our recent pursuit of the design and synthesis of novel chiral ligands, we have found an excellent opportunity both to test these hypothesis and to develop a class of highly effective chiral phosphinite ligands. Our new chiral phosphinite ligands, namely 1(*R*),5(*R*),6(*R*)-1,6-bis(diphenylphosphinoxy)spiro[4.4]-nonane (abbreviated *R*-spirOP, **1**) and 1(*S*),5(*S*),6(*S*)-1,6-bis-(diphenylphosphinoxy)spiro[4.4]nonane (abbreviated *S*-spirOP, **2**) are based on the use of a rigid spiro backbone which mimics the binaphthyl rings in BINAP in its influential state (skewed position). Since the spiro backbone is totally rigid, the small

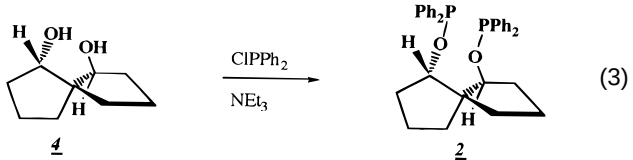


1 *R*- spirOP *2* *S*- spirOP

amount of conformational flexibility in the C−O−P bond in **1** (or **2**) is not expected to cause too many problems. This rationale was strongly supported by our experimental results. Compounds **1** and **2** were conveniently prepared through the reaction of chlorodiphenylphosphine with the corresponding spiro diols **3** and **4**.[9]



3 *1* (2)



4 *2* (3)

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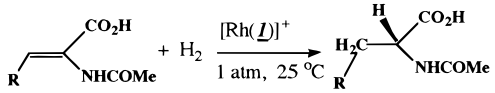
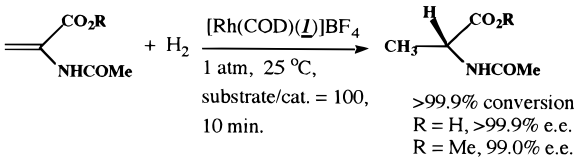
Table 1. The Rh(**1**)$^+$-Catalyzed Asymmetric Hydrogenation of (*Z*)-2-Acetamido-3-arylacrylic Acids[a]



entry	substrate (R =)	ee (%)[b]
1	Ph	97.9
2	4-Cl-Ph	97.3
3	2-Cl-Ph	97.3
4	3-Cl-Ph	97.4
5	4-NO_2-Ph	97.0

[a] Reaction conditions: 1 atm of H_2; ambient temperature; 10 min reaction time; substrate/catalyst = 100 (M/M); solvent = methanol; >99.9% conversion was observed in all cases. [b] The ee values were determined by chiral GLC with a Chrompack Chirasil-L-Val column after converting the products to the corresponding methyl esters. The *R* configuration was obtained for all products. Same results were obtained when Rh(**2**)$^+$ was used as catalyst except that all products were in the *S* configuration.

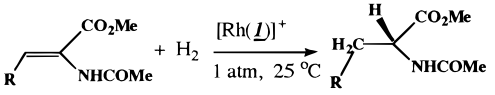
When a cationic rhodium catalyst containing **1** (or **2**) was used in the asymmetric hydrogenation of 2-acetamidoacrylic acid at ambient temperature and under 1 atm of H_2, the desired 2-acetamidopropionic acid was obtained in >99.9% conversion and >99.9% enantiomeric excess (ee). Under similar conditions, the asymmetric hydrogenation of the methyl ester of 2-acetamidoacrylic acid gave >99.9% conversion to the corresponding hydrogenation product in 99.0% ee. These results

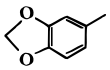


(4)

compared very favorably with the best known chiral phosphine-rhodium catalysts. For example, the ee values (%) of the asymmetric hydrogenation of 2-acetamidoacrylic acid reported in the literature are as follows:[10−12] DIPAMP, 94; DIOP, 73; CHIRAPHOS, 91; BPPM, 98.5; BINAP, 67; BICP, 97.5; Et-DuPHOS, 99.4. The rate of reaction with this new rhodium−phosphinite catalyst was also very fast. When a substrate/catalyst ratio of 10 000 was used and when the reaction was carried out at ambient temperature under 200 psig H_2, >99.9% conversion of 2-acetamidoacrylic acid to 2-acetamidopropionic acid (96.8% ee) was observed in 1 h. Further studies of the use of Rh(**1**)$^+$ [or Rh(**2**)$^+$] in the asymmetric hydrogenation of other prochiral enamides confirmed that the high enantioselectivity of the catalyst was quite general. A variety of (*Z*)-2-acetamido-3-arylacrylic acids were hydrogenated with this catalyst and in all cases the desired products were found to have ee values of over 97%. More detailed data are summarized in Table 1. Again, these results compared very well with those obtained with the well-known chiral phosphine−rhodium catalysts. For example, the ee values (%) of the asymmetric hydrogenation of (*Z*)-2-acetamidocinnamic acid reported in the literature are as follows:[10−12] DIPAMP, 95; DIOP, 81; CHIRAPHOS, 89; BPPM, 91; BINAP, 84; BICP, 96.8; Et-DuPHOS, 99.

Table 2. The Rh(**1**)$^+$-Catalyzed Asymmetric Hydrogenation of (*Z*)-2-Acetamido-3-arylacrylic Acid Methyl Esters[a]



entry	substrate (R =)	ee (%)[b]
1	Ph	95.7
2	4-Cl-Ph	94.2
3	4-F-Ph	95.5
4	4-Br-Ph	96.3
5	4-MeO-Ph	96.2
6	4-Me-Ph	95.6
7		97.2
8		94.9

[a] Reaction conditions: 1 atm of H_2; ambient temperature; 10 min reaction time; substrate/catalyst = 100 (M/M); solvent = methanol; >99.9% conversion was obtained in all cases. [b] The ee values were determined by chiral GLC with a Chrompack Chirasil-L-Val column. The *R* configuration was obtained for all products. Same results were obtained when Rh(**2**)$^+$ was used as catalyst except that all products were in the *S* configuration.

The enantioselectivity of Rh(**1**)$^+$ [or Rh(**2**)$^+$] in the asymmetric hydrogenation of the methyl esters of (*Z*)-2-acetamido-3-arylacrylic acids was also found to be very high (Table 2). These results clearly show the high potential for the general application of these catalysts in the asymmetric hydrogenation of prochiral enamides. More importantly, these results also shed light on the design of enantioselective chiral phosphinite catalysts: the use of a rigid backbone to compensate for the excess of flexibility caused by the C−O−P bonds in the phosphinite can significantly improve the enantioselectivity of the chiral catalysts. This understanding opens a new frontier for the design and synthesis of simple and selective catalysts.

It is of interest to note that although phosphinites are considered to be unstable in protic solvents, in this study we have found both Rh(**1**)$^+$ and Rh(**2**)$^+$ to be quite stable in methanol solution. On the basis of the results of a ^{31}P NMR study, there was no appreciable decomposition of the complexes in methanol at ambient temperature for 2 days. Since the turnover rates of hydrogenation were extremely fast, the stability of these complexes during reaction was certainly not a problem.

In conclusion, we have developed a novel, highly effective chiral phosphinite ligand for the catalytic asymmetric hydrogenation of enamides. The remarkably high catalytic activity and enantioselectivity of its rhodium complex for the hydrogenation of a variety of prochiral enamides indicated a good potential for wide application of this class of catalysts. Further studies of other transition metal complexes of this ligand and their application in asymmetric catalytic reactions are in progress.

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Supporting Information Available: NMR spectra of **1**, GLC chromatograms of the chiral products, and experimental procedures including the preparation of **1** and the procedure for hydrogenation (16 pages). See any current masthead page for ordering and Internet access instructions.

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